REMARKS

Claims 1-25, 28-40, and 48-56 are pending in the present application. Claims 1, 13, 17, 18, 22, and 23 have been amended without prejudice and without acquiescence to clarify the scope of the invention. Claims 26 and 27 are withdrawn. Claims 57-60 have been added. Support for these claims can be found throughout the entire specification and the original. Yet further, Applicants have also included an abstract, which is similar to the abstract in the original PCT application. Applicants assert that no new matter has been added.

The issues outstanding in this application are as follows:

- Claims 1-25, 28-40 and 48-56 were rejected under 35 U.S.C. § 101 as allegedly lacking an specific or well-established utility.

- Claims 6, 7, 25, 30, 31, 34, and 35 were rejected under 35 U.S.C. § 112, second paragraph.

- Claims 1-25, 28-40 and 48-56 were rejected under 35 U.S.C. § 112, first paragraph.

- Claims 1-5, 8-24, 28, 29, 33, 37-39 and 48-56 were rejected under 35 U.S.C. § 102 (e) as being anticipated by Palese et al. (US Pat. No. 6022726).

- Claims 1-5, 8, 9, 12-18, 20-24, 29, 33 and 37 were rejected under 35 U.S.C. § 102 (b) as being anticipated by Bergmann et al. (J. General Virology, 1995).

- Claims 1-25 and 28-40 were rejected under 35 U.S.C. 103(a) as being unpatentable over Bergmann et al. (J. General Virology, 1995); Bergmann et al. (Virus Research, 1996); and Kim et al. (J. General Virology, 1997) in view of Castrucci et al. (J. Virology 1992).

- Claims 1-5, 8-24, 28, 29, 33, 37-39, 48-56 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of US Pat. No. 6022726.

Applicants respectfully traverse the outstanding rejections, and Applicants respectfully request reconsideration and withdrawal thereof in light of the amendments and remarks contained herein.

I. Rejection under 35 U.S.C. § 101

Claims 1-25, 28-40 and 48-56 are rejected under 35 U.S.C. § 101 as lacking a specific or well established utility. Applicants respectfully traverse.

Under the utility guidelines, the initial burden is on the Patent Office to establish a *prima facie* case of utility, which requires sufficient evidentiary basis. According to MPEP 2107.02, where the asserted utility is not specific or substantial, a *prima facie* showing contains the following:

1) An explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed invention is neither both specific and substantial nor well-established;

2) Support for factual findings relied upon reaching this conclusion; and

3) An evaluation of all relevant evidence of record, including utilities taught in the closest prior art.

Applicants assert that the Office has not properly established a *prima facie* case. The Examiner has suggested that the attenuated viruses in accordance with the present invention which contain a mutation in the duplex region are not adequately distinguished from viruses in nature that mutate over time. Applicants submit that this is not correct, in particular given the nature and position of the mutation that is claimed in accordance with the present invention. In more detail, the claims of the present invention relate to an influenza virus that has been mutated in the duplex non-coding region. This is a short structural component of the influenza virus, a region of the 5' genomic segment base pairs with a region of the 3' segment. As explained in the specification, the double stranded region of the promoter of an influenza A vRNA segment consists of 5 to 8 base pairs. This segment is highly conserved. Similarly, the 3' and 5' non-coding terminal sequences of influenza B and C vRNA are also

highly conserved and also show partial inverted complementarity. Thus, in the influenza viruses, the 5' and 3' ends of the viral RNA segment form a duplex with base pairing between the 5' and 3' terminal sequences of a single strand. The sequences have also been shown to be highly conserved between different segments of influenza.

The present invention requires effectively at least a double mutation that is a mutation in the 5' region and the 3' region, at two bases that would normally pair with each other. While there may be some mutation in influenza viruses, it is highly unlikely that a wild type influenza would incorporate two mutations at the precise location that would normally allow their base pairing to occur. Given that the nucleotides that are involved in base pairing are present at remote sites on the viral segment, the ability of these terminal regions to base pair would not increase the chances of such a double mutation occurring.

In view of the above statements, Applicants assert that the specification does disclose the term mutated, more specifically mutated duplex region (see page 5, lns, 15-18), and thus, sets forth a specific and substantial utility and/or a well-established utility. If, however, the Examiner continues to maintain a *prima facie* case of non-utility, then the Applicants respectfully request that the above criteria be indicted in the next Action, more specifically support for factual findings relied upon in reaching this conclusion; and an evaluation of all relevant evidence of record, including utilities taught in the closest prior art. Applicants remind the Examiner that if the Office cannot develop a proper *prima facie* case and provide evidentiary support for a rejection under 35 U.S.C. 101, then a rejection on this ground should not be imposed. See, for example, *In re Oetiker,* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

Yet further, Applicants assert that the 35 U.S.C. 101 rejection is improper and respectfully request that the rejection be withdrawn. As indicated by the courts and the MPEP 2107.01 part IV, if a rejection is properly imposed under 35 U.S.C. 101 it should be accompanied with a rejection under 35 U.S.C. 112, first paragraph. See *In re Brana* 51 F. 3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). Upon review of the Official Action, it appears that the Examiner did not impose the appropriate 35 U.S.C. 112 rejection that is to accompany the 35 U.S.C. 101. In view of the lack of the 35 U.S.C. 112 rejection, Applicants assert that the 35 U.S.C. 101 rejection is improper and request that it be withdrawn.

II. **Rejection under 35 U.S.C. § 112**

A. Second Paragraph

Claims 6, 7, 25, 30, 31, 34 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Applicants traverse.

As has been explained above section under the arguments relating to the 101 rejection, the viral segment under consideration is highly conserved. In all influenza A virus viral segments, the bases under consideration in claim 6 have the same position from the 3' terminus and 5' terminus in each segment. Thus, in the context of influenza viruses and in particular the fact that these viruses are highly conserved in this non-coding region and the fact that the nucleotide positions are defined from the terminus, the Applicants assert that there is any need to further define the influenza A virus structure. Thus, in contrary to the position taken by the Examiner, the influenza viral structures available to one of skill in the art do have the required structure and will, for example have adenine at position 11 from the 5' terminus.

In view of this argument, Applicants respectfully request that the rejection be withdrawn.

B. First Paragraph

Claims 1-25, 28-40 and 48-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific mutation of D1, D2, D3, and D1/2, does not reasonable provide enablement for predicting the effect of mutations having "functional modifications" or "functional equivalent substitutions at the same position". Applicants traverse.

The Examiner has argued that Flick et al shows that some substitutions resulted in greater CAT activity. It is difficult to see how Flick et al is relevant to the present claims. Figure 4 referred to by the Examiner provides a summary of expression rates for single-nucleotide substitution derivatives. As has been explained above, the present invention is not concerned with single-nucleotide substitutions, but with one or two base-pair substitutions,

that is effectively two substitutions in each base pair and thus at the very least, two nucleotide substitutions in any viral segment.

In order to advance prosecution of the present application, Applicants have amended the claims without prejudice and without acquiescence to delete the reference to the functional modification of the protein. One of skill in the art would in any event understand from the claims and the present application as a whole that attenuation at least some level is achieved through mutations in non-coding regions, as compared to an influenza virus that has not been mutated in this region, regardless of the nature of the protein that is encoded by the sequence linked to that non-coding region.

The Examiner has suggested that there is a concern that a single mutation can result in a reversion to the original viral sequence. However, as has been discussed in some detail above, the claims are not directed to single mutations. The claims encompass at least a double mutation. The mutations occur in the 5' terminal region and the 3' terminal region. In view of this double mutation, at isolated ends of the viral segment, there is a substantially reduced concern that there will be any reversion to the original viral sequence.

In light of the amendments and arguments, Applicants request that the rejection be withdrawn.

III. **Rejection under 35 U.S.C. § 102**

A. Palese et al. (US Pat. No. 6022726)

Claims 1-5, 8-24, 28, 29, 33, 37-39, and 48-56 are rejected under 35 U.S.C. 102(e) as being anticipated by Palese et al. (US Pat. No. 6022726). Applicants traverse.

Anticipation of a claim is only established where "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed.Cir. 1987).

Applicants assert that Palese US Pat. No. 6022726 teaches influenza viruses in which segments of the non-coding region have been substituted between different influenza types

thereby producing a chimeric virus. The present invention relates to mutations, e.g., base pair substitutions, occurring in the duplex non-coding region; this is not similar to a chimeric virus. Although Palese et al makes reference to potential mutated viral segments being produced, Table III referred to in Example 7 on column 16 is missing from US Patent No. 6022726. Thus one of skill in the art is not provided with any indication in Palese et al of the mutations that were prepared nor of the activity that was achieved. Thus, the only relevant disclosure in Palese et al relates to the production of chimeric influenza viruses in which segments of influenza B were substituted into influenza A. Thus, the claims are not anticipated, and Applicants respectfully request that the rejection be withdrawn.

B. Palese et al. (WO 93/21306)

Claims 1-5, 8-24, 28, 29, 33, 37-39, and 48-56 are rejected under 35 U.S.C. 102(e) as being anticipated by Palese et al. (WO 93/21306). Applicants traverse.

Anticipation of a claim is only established where "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed.Cir. 1987).

Similar to Palse US Pat. No. 6022726, Palese WO 93/21306 teaches influenza viruses in which segments of the non-coding region have been substituted between different influenza types thereby producing a chimeric virus. The present invention relates to mutations, e.g., base pair substitutions, occurring in the duplex non-coding region; this is not similar to a chimeric virus. Although Palese et al makes reference to potential mutated viral segments being produced, Table III referred to in Example 7 page 33 is also missing in Palese WO 93/21306 similar to Palese US Pat. No. 6022726. Thus one of skill in the art is not provided with any indication in Palese et al of the mutations that were prepared nor of the activity that was achieved. Thus, the only relevant disclosure in Palese et al relates to the production of chimeric influenza viruses in which segments of influenza B were substituted into influenza A. Thus, the claims are not anticipated, and Applicants respectfully request that the rejection be withdrawn.

C. Rejection under 35 U.S.C. § 102

Claims 1-5, 8, 9, 12-18, 20-24, 28, 29, 33 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Bergmann et al. (J. of General Virology, 1995). Applicants traverse.

Anticipation of a claim is only established where "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed.Cir. 1987).

Applicants assert that Bergmann et al. teaches production of chimeric influenza viruses in which segments of influenza B are substituted into influenza A, which is not similar to the present invention. The present invention relates to a mutated duplex region; not a chimeric region. Thus, Bergmann et al. does not teach each and every element of the claims and Applicants respectfully request that the rejection be withdrawn.

IV. **Rejection under 35 U.S.C. § 103**

Claims 1-25 and 28-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bergmann et al. (J. General Virology, 1995); Bergmann et al. (Virus Research, 1996); and Kim et al. (J. General Virology, 1997) in view of Castrucci et al. (J. Virology 1992). Applicants traverse.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

Applicants assert that Bergmann et al. 1995 teaches production of chimeric influenza viruses in which segments of influenza B are substituted into influenza A, which is not similar to the present invention. The present invention relates to a mutated duplex region; not a chimeric region.

Still further, Bergmann et al. 1996 teaches production of mutated influenza viruses in which mutations are made in nonconserved non-coding nucleotides. This is not similar to the

present invention; in fact it is the opposite of the present invention, in which mutations are performed in the conserved non-coding duplex region.

It can be seen from the description of the present application, that the claims are not intended to encompass such chimeric versions, nor encompass mutations occurring in non-conserved regions. Applicants assert that none of the cited documents disclose any viral segment in which only one or two base pair mutations (that is two or four mutations in total) are present in the non coding duplex region. Even if a chimeric influenza virus could be considered to be a mutated virus, which is not admitted, such chimeric viruses clearly include many more changes than a single or double base pair mutation. Similarly, none of these documents suggest mutations at position 10' or 11' from the 3' terminal end or at 11' or 12' from the 5' terminal end.

None of the documents cited by the Examiner teaches the base pair mutations and certainly do not suggest that attenuation could be achieved by base pair mutation at one or two locations in the 3' or 5' terminal ends. For the first time, in the present application, single base pair mutations of the vRNA promoter were studied. These data prove definitively that specific base pair mutations cause attenuation. Thus, the present application demonstrates that specific base pair mutations in the vRNA promoter cause attenuation. The production of chimeric influenza viral segments does not allow one of skill in the art to make any firm conclusions in relation to the effect of one or two base pair mutations in the promoter as now claimed.

Kim et al is concerned purely with investigations into the structure of the promoter using a CAT reporter. The paper itself makes no conclusions concerning the possibility of using such mutations in order to produce attenuated viruses. As noted by the Examiner, the reference does not teach the correlation of reduced protein expression within an attenuated phenotype. The Examiner has suggested that it would have been obvious to one of skill in the art to utilize the mutations described in Kim et al to reduce expression taught, for example by Bergmann et al. However, Kim et al was written at a time when Bergmann was available and indeed much work had been carried out in this field relating to attenuation of the influenza phenotype. Similar work is cited in the paper by Kim et al. For example, reference is made to Luo et al Journal of Virology 66, 4679 4685, 1992 and Muster et al PNAS 88,

5177 5181, 1991 in the Kim et al each of which relate to chimeric influenza A/B viruses and examine attenuation of the viruses in those chimeras. Notwithstanding this, there is nothing in Kim to suggest that the mutations described therein might be useful in the provision of attenuated viruses.

Thus, neither Bergmann et al. 1995 nor Bergmann et al. 1996 separately or in combination teach or suggest all of the limitations of the pending claims. Yet further, the addition of Kim et al. and Castrucci et al. do not remedy the deficiencies of either Bergmann 1995 or 1996, thus, Applicants assert that the examiner has not established a *prima facie* case of obviousness, and respectfully request that the rejection be withdrawn.

V. Rejection under Double Patenting

Claims 1-5, 8-24, 28, 29, 33, 37-39, and 48-56 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1-10 of US Pat. No. 6022726. Applicants traverse.

Applicants refer the Examiner to the above arguments, which clearly indicate that the present invention is considered to be patentably distinct from US Patent No. 6022726. Thus, Applicants request that the double patenting rejection be withdrawn.

CONCLUSION

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. HO-P02074US0 from which the undersigned is authorized to draw.

Dated: September 24, 2004

Respectfully submitted,

By _____

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